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Examining the relationship between the oral microbiome, alcohol intake and alcohol-comorbid neuropsychological disorders: protocol for a scoping review

Katherine A. Maki, Chelsea B. Crayton, Gisela Butera, Gwyneth R. Wallen

ABSTRACT

Introduction Heavy alcohol use and alcohol use disorder (AUD) continues to rise as a public health problem and increases the risk for disease. Elevated rates of anxiety, depression, sleep disruption and stress are associated with alcohol use. Symptoms may progress to diagnosed neuropsychological conditions and increase risk for relapse if abstinence is attempted. Research on mechanisms connecting the gastrointestinal microbiome to neuropsychological disorders through the gut-brain axis is well-established. Less is known about the oral microbiome and oral microbial-associated biomarkers may signal to the brain. Therefore, a synthesis of research studying relationships between alcohol intake, alcohol-associated neuropsychological symptoms and the oral microbiome is needed to understand the state of the current science. In this paper, we outline our protocol to collect, evaluate and synthesize research focused on associations between alcohol intake and AUD-related neuropsychological disorders with the oral microbiome.

Methods and analysis The search strategy was developed and will be executed in collaboration with a medical research librarian. Studies will be screened by two independent investigators according to the aim of the scoping review, along with the outlined exclusion and inclusion criteria. After screening, data will be extracted and synthesized from the included papers according to predefined demographic, clinical and microbiome methodology metrics.

Ethics and dissemination A scoping review of primary sources is needed to synthesize the data on relationships between alcohol use, neuropsychological conditions associated with AUD and the oral microbiome. The proposed scoping review is based on the data from publicly available databases and does not require ethical approval. We expect the results of this synthesis to identify gaps in the growing literature and highlight potential mechanisms linking the oral-brain axis to addiction and other associated neuropsychological conditions. The study findings and results will be disseminated through journals and conferences related to psychology, neuroscience, dentistry and the microbiome.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We outline a systematic synthesis of predefined global community and specific bacterial microbiome metrics to facilitate comparison across primary sources focused on different levels of alcohol use and its associated conditions/symptoms including anxiety, depression, sleep disruption and stress or stress-associated disorders.

⇒ Not all oral microbiome metrics that are standard in the field can be included in the data extraction form as we are limited to what the authors of the primary sources report in their main paper or supplemental data. Data from other oral microbiome organisms (ie, virus, protozoa, archaea, etc) will not be synthesized in this review.

⇒ Preclinical and translational clinical study results will be compared with evaluate agreement and contrasting results between animal and human studies.

⇒ Validated frameworks for reviews including the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guideline are used to organise the reporting of the current protocol paper and future scoping review paper, respectively.

⇒ Environmental factors and modifiers of the oral microbiome community structure, such as smoking and other health behaviours, will be captured in the literature synthesis to inform future research protocols.

INTRODUCTION

Heavy alcohol use and alcohol use disorder

Heavy use of alcohol and alcohol use disorder (AUD) is pervasive with 14.5 million Americans meeting criteria for AUD in 2019. According to research from the National Institute on Alcohol Abuse and Alcoholism, alcohol use in the USA has increased by 2.2% every year since the start of the 1990s. This trend is expected to continue and be exacerbated by social and economic conditions.

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created by the COVID-19 pandemic. AUD is a condition characterised by an individual's inability to stop and/or control their alcohol use even when faced with health, occupational and social consequences. AUD is associated with permanent change to an individual's psychological and physiological homeostasis, with many individuals becoming physically dependent on continued alcohol consumption to function and perform activities of daily living. Heavy alcohol use is also tied to chronic health conditions encompassing multiple organ systems often leading to liver, cardiovascular and neurological disease. Consequently, 3 million deaths per year are associated with AUD worldwide.

Neuropsychological disorders associated with AUD
There are numerous neuropsychological symptoms and disorders that are frequent in patients with AUD in addition to the previously reported mortality and chronic health disorders associated with AUD. Many of these disorders are the result of early life stress and chronic stress exposure that can contribute to alcohol use, cause the onset of AUD or exacerbate pre-existing heavy alcohol use. Not only do these neuropsychological disorders increase the predisposition for alcohol consumption and AUD, but ongoing heavy alcohol use is associated with an increase in symptoms related to these neuropsychological disorders. Common neuropsychological comorbid conditions associated with ongoing heavy alcohol use and AUD include anxiety, depression, sleep disturbance and altered stress handling including an increased risk for post-traumatic stress disorder (PTSD; see table 1 for operational definitions of these conditions).

Anxiety disorders are one of the most common neuropsychological disorders with one in four US adults meeting the diagnostic criteria for an anxiety disorder every year. People with anxiety, specifically social anxiety, look for ways to alleviate negative symptoms and turn to substance use to cope with the unpleasant associated manifestations. In populations of treatment-seeking individuals with AUD, up to 50% of subjects met the criteria for one or more anxiety disorders including social phobias, obsessive compulsive disorder and generalised anxiety. Following anxiety, depression is the second most common mental health disorder in the USA with 8.4% of US adults experiencing it every year. In populations of individuals with AUD, this rate increases to over 50% with co-occurring major depressive disorder being the most common co-occurring neuropsychological disorder in subjects with heavy alcohol use. In longitudinal studies of major depressive disorder and AUD co-occurrence from adolescence to adulthood, major depressive disorder precedes AUD 57% of the time, while AUD precedes major depressive disorder 41% of the time, and initial co-occurrence only occurs in 2% of subjects. Given this co-occurrence, evidence suggests that depressive and anxiety disorders have a bidirectional relationship with AUD, where an increase in severity in one disorder results in an increase in severity in the other regardless of which disorder occurred first.

Other neuropsychological conditions that increase the risk for heavy alcohol use and AUD include sleep disorders and PTSD. Sleep disturbances impact around 30% of the US population each year, with between 10% and 20% experiencing chronic insomnia. Insomnia has been observed in up to 91% of populations of treatment-seeking individuals with AUD. Temporal research focusing on timing of sleep issues and the onset of AUD has found that sleep disturbance precedes diagnoses of AUD and can contribute to initial and ongoing alcohol consumption amount or frequency. As alcohol is a sedative, individuals experiencing chronic sleep disturbances often use alcohol as a sleep aid to decrease sleep latency and fall asleep faster. However, physiological sleep is negatively impacted by alcohol use as alcohol consumption before bed increases sleep fragmentation, snoring, nightmares and symptoms of insomnia later in the night. Furthermore, in treatment-seeking patients with AUD, lower sleep quality and sleep regularity were associated with a greater risk of relapse post-AUD treatment, suggesting sleep is an important predisposing factor to alcohol use and AUD. Like disrupted sleep, increased or pervasive episodes of stress can predispose subjects to increased alcohol use and AUD. Approximately 70% of the US population has encountered at least one traumatic event, and 1 in 13 Americans will develop PTSD in their lifetime. A diagnosis of PTSD is more frequent in women, and women are two times as likely to have a diagnosis of PTSD versus men. PTSD and the risk for substance abuse and AUD have been reported in the literature as early as the 1970s, finding that individuals who developed PTSD were more likely to have issues with heavy alcohol use, and an estimated 35%–50% of individuals that meet the criteria for AUD have co-occurring PTSD. Individuals with PTSD and AUD often experience a feedback loop where flashbacks trigger the urge to drink but the drink in turn exacerbates the severity of the flashback after the effects of alcohol wears off causing the individual to drink again.

Aside from neuropsychological disorders that predispose individuals to AUD, ongoing heavy alcohol use is associated with increased symptom severity of the same disorders that predispose subjects to increased alcohol consumption, including stress and stress-associated symptoms of anxiety, depression and disrupted sleep.

When processed by the body, alcohol acts as a central nervous system depressant decreasing motor control, impacting memory and dysregulating the physiological stress response. Once the effects of alcohol subside, the central nervous system is reactivated causing an increase in inflammation and activation of the hypothalamic-pituitary-adrenal axis. With the hypothalamic-pituitary-adrenal axis reactivated, there is an increase in the release of cortisol and general inflammation, which is linked to an increase in neuropsychological symptoms and dysregulation of the gut-brain system.
### Table 1  Operational definitions

<table>
<thead>
<tr>
<th>AUD and alcohol-comorbid symptoms/disorders</th>
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<tbody>
<tr>
<td><strong>AUD</strong></td>
<td>A medical condition characterised by the inability to control and/or stop excessive alcohol use despite occupational, social and health consequences.5</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>An emotion triggered by real or perceived threats characterised by feelings of excessive worry, unease and the activation of the sympathetic nervous system. This emotion can manifest into a diagnosed mood disorder.80</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>A mood disorder characterised by persistent sadness, pessimistic affect, fatigue and loss of interest in activities typically associated with pleasure.96 Helplessness experienced due to this disorder impacts an individual’s ability to complete activities of daily life</td>
</tr>
<tr>
<td><strong>Sleep disturbance</strong></td>
<td>A group of disorders that are characterised by dysfunction in initiating and maintaining sleep, a maladaptive sleep schedule, and abnormalities in physiological arousal while asleep.87</td>
</tr>
<tr>
<td><strong>Stress/PTSD</strong></td>
<td>A stress disorder characterised by an individual reliving a traumatic event through recurrent flashbacks and/or dreams that causes an avoidance of reminders of the event, and is associated with increased physiological arousal and a general negative affect.84</td>
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### Microbiome

#### Sequencing methodology

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Description</th>
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<tbody>
<tr>
<td>16S rRNA gene amplicon sequencing</td>
<td>A microbiome sequencing method that uses PCR amplification to analyse variable regions of 16S rRNA gene to identify bacteria in a sample.98</td>
</tr>
<tr>
<td>Shotgun metagenomics sequencing</td>
<td>A microbiome sequencing method that takes all genomic DNA from a sample and sequences it by breaking DNA down into individual fragments. This can be used for functional profiling and often produces a greater taxonomic resolution than 16S rRNA sequencing.99</td>
</tr>
</tbody>
</table>

#### Microbiome and microbiome-associated data items (synthesis table columns)

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Alpha diversity</strong></td>
<td>A measure of diversity that provides insight into the profile of an ecological community using estimates of a sample’s richness, evenness or both.100 Frequently used estimators include:</td>
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<tr>
<td></td>
<td>► Shannon’s index</td>
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<tr>
<td></td>
<td>► Observed taxa</td>
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<tr>
<td></td>
<td>► Simpson’s index</td>
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<tr>
<td></td>
<td>► Phylogenetic diversity: Faith’s phylogenetic distance</td>
</tr>
<tr>
<td><strong>Beta diversity</strong></td>
<td>A measure of diversity that estimates differences and similarities between bacterial samples.101 Estimators include:</td>
</tr>
<tr>
<td></td>
<td>► Aitchison distance</td>
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<tr>
<td></td>
<td>► Bray-Curtis dissimilarity</td>
</tr>
<tr>
<td></td>
<td>► Phylogenetic-based measures: weighted or unweighted UniFrac</td>
</tr>
<tr>
<td></td>
<td>► Can be visualised through NMDS, PCoA or UMAP plots in 2D or 3D manner</td>
</tr>
<tr>
<td><strong>Global phylum changes</strong></td>
<td>The taxonomic level of phylum is the highest taxonomic class of bacteria.102 Changes that occur at the phylum level in bacterial communities represent broader community change in response to an intervention or in association with a condition. Generally described through the Firmicutes:Bacteroidetes ratio.103</td>
</tr>
<tr>
<td><strong>Differential abundance</strong></td>
<td>A measure of difference that uses the abundance of each individual bacteria for comparison across conditions (i.e., intervention group vs control or within group across time).104 Differential abundance analysis can be performed at higher or lower order taxonomic levels including family, genus or species (among others), depending on the sequencing technology. Analysis methods include:</td>
</tr>
<tr>
<td></td>
<td>► ANCOM</td>
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<td></td>
<td>► ALDEx2</td>
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<td></td>
<td>► DESeq2</td>
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<td></td>
<td>► EdgeR</td>
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<td></td>
<td>► LEfSe</td>
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Continued
axis. Gut-brain communication and gut microbiome-associated mechanisms linking stress and inflammation to anxiety, depression and sleep disturbance have been well documented in the literature in both preclinical and human translational studies. However, it is unclear whether similar microbe-brain communication mechanisms are replicated in other niches in the body with high microbial activity, such as the oral cavity.

**Oral microbiome**

The human body serves as a host for a number of complex microbial environments that house bacteria responsible for performing functions that maintain everyday bodily functions. These bacteria, commonly referred to as the human microbiome, consist of viruses, fungi, bacteria and archaea that coexist and inhabit the human body and their genes. Much of the current research on these microbial communities focuses on the gut microbiome and its relationship to the brain through the gut-brain axis. Despite a primary focus on the gut-brain axis related to microbe to brain signalling, there is research venturing into the exploration of associations between the oral microbiome and mental health.

The oral microbiome is the second most diverse bacterial ecosystem in the human body and consists of several niches across different surfaces of the mouth; each with their own unique microbial makeup. Each person has an individualised microbiome that changes over the life course and is formed by genetic, environmental, dietary and health behaviours. The oral microbiome plays a key role in several important physiological processes including regulating inflammation, preventing the growth of diseases and facilitating digestion. When the ecosystem of these microbial communities is altered in association with various internal and external insults, the oral microbiome is then associated with an increased incidence of local conditions (ie, periodontitis) and systemic disease including diabetes mellitus, cardiovascular diseases and oesophageal cancer.

Current research focuses on the importance of the oral microbiome and overall health through examining periodontitis and risk factors related to oral decay. One key risk factor for developing periodontal disease is alcohol use, as chronic heavy alcohol use alters the oral environment. Specifically, heavy alcohol use is associated with reduced saliva production, disruption of the tooth enamel, and lower oral pH all of which contribute to an increase in dental caries and oral inflammation. AUD and oral health are so closely tied to one another that in a study of treatment-seeking in patient individuals with AUD, it was found that oral health (quantified by the modified Beck’s Oral Assessment Scale) and alpha diversity of the oral microbiome linearly decreased over their course of treatment with abstinence from alcohol. Given the independent connection of AUD with both neuropsychological disorders and oral health, one might hypothesise that the oral microbiome may act as a signalling

<table>
<thead>
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<th>Table 1 Continued</th>
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<tbody>
<tr>
<td><strong>Functional gene prediction</strong></td>
</tr>
<tr>
<td><strong>Metabolomics</strong></td>
</tr>
<tr>
<td><strong>Cytokine/immune markers</strong></td>
</tr>
<tr>
<td><strong>Markers of stress</strong></td>
</tr>
</tbody>
</table>

ALDEex2, analysis of variance-like differential expression version 2; ANCOM, analysis of compositions of microbiomes; AUD, alcohol use disorder; EdgeR, empirical analysis of digital gene expression in R; IL, interleukin; KEGG, kyoto encyclopedia of genes and genomes; LEfSe, linear discriminant analysis effect size; NMDS, non-metric multidimensional scaling; PCoA, principal coordinates analysis; PICRUST, phylogenetic investigation of communities by reconstruction of unobserved states; PTSD, post-traumatic stress disorder; 16S rRNA, 16S ribosomal RNA; TNF, tumour necrosis factor; UMAP, uniform manifold approximation and projection.
mediator between oral health and neuropsychological manifestations, providing a better understanding of how the microbial environment influences the brain.76–78

**Oral-brain axis**

The oral-brain axis is a theory regarding the connection between oral health, the oral microbiome and neurophysiological-associated processes and symptoms.76–78 At its core, the oral-brain axis theory is rooted in the belief that chemical mechanisms, facilitated by bacteria in the mouth, may influence chemical mechanisms and signalling pathways in the brain.76–78 Nevertheless, current research focused on relationships between the oral microbiome and neurophysiology are still unknown. There is evidence of communication from the brain to the oral environment in paediatric dental research and developmental psychology research where adverse childhood experiences and increased stress are associated with oral health alterations.87–91 For example, adolescent health research has found that children with externalised stress responses often experience increased oral pain, oral ulcers and dental caries.87–91 As more literature is published tying these oral-associated stress responses to the oral microbiome, it is expected that microbial compositional changes may mirror changes in oral health, similar to what has been seen in paired longitudinal oral-microbial responses as patients with AUD undergo treatment.86 Longitudinal studies of how changes in the oral microbiome modulate neurophysiological symptoms are also lacking in the literature. Before designing longitudinal studies to investigate potential mechanisms in oral-brain communication, and how this may be altered by heavy alcohol use, an understanding of which oral microbiome-associated features are impacted by alcohol use is needed. Therefore, a systematic synthesis of primary sources investigating relationships between the oral microbiome, alcohol use and AUD-associated symptoms is needed for rigorous hypothesis-driven and clinically relevant future research studies.

**Aims**

The aim of this paper is to outline a protocol for a scoping review to examine and synthesise research on the relationship between the oral microbiome and alcohol use, along with common comorbid neuropsychological disorders and related symptoms in AUD: anxiety, depression, sleep disturbance and altered stress handling. Based on the findings of this scoping review, we hope to gain insight into the extent of how alcohol and its associated neuropsychological symptoms/disorders relate to the oral microbiome, the methods used to characterise the clinical and oral microbiome phenotypes of interest, and the possible translational applications of this research.

**METHODS AND ANALYSIS**

**Protocol design**

A scoping review of the currently published literature was chosen due to the different alcohol-associated neuropsychological disorders and symptoms of interest, along with the variability of oral microbiome metrics reported in the literature, so comprehensive sources can be synthesised in human and preclinical data. The protocol for this scoping review is informed by methodology outlined in published scoping review frameworks,92 93 and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines will be used to facilitate the reporting of the search strategy, source selection and analysis/synthesis of primary sources in this protocol paper.94 Briefly, identifying the overarching research question and specific research objectives, identifying relevant sources through an electronic search strategy across multiple databases, source selection, and data extraction and synthesis of results will be outlined. The protocol for this scoping review is registered on Open Science Framework (osf.io) and can be accessed at https://osf.io/qz2hy/ (DOI: 10.17605/OSF.IO/QZ2HY). The scoping review procedures including literature search, data extraction and source synthesis are planned to occur between February 2024 and December 2024.

**Identifying the research question**

The overarching research question for this scoping review is: what are the associations between alcohol consumption and alcohol-associated neuropsychological disorders with the bacterial oral microbiome in preclinical and translational human research studies? Subresearch questions with specific examples are presented in table 2, and operationalised definitions used to formulate the research questions are listed in table 1.

**Eligibility criteria**

**Inclusion criteria**

- Primary research published in peer-reviewed journals will be included. Additionally, papers housed on preprint servers, and conference proceedings/abstracts that adequately address the overarching research question will be included in this study. If a preprint paper or conference abstract is included in the final scoping review, a notation will be made in the summary of included evidence table that the paper has not been peer-reviewed.

- All study designs will be included in this scoping review as well as human and rodent studies (preclinical research). Subjects of all ages will be considered, and no date limits will be set in the search strategy. There will be no limits placed on language (ie, sources published in all languages will be considered), but if we are not able to retrieve an English version or obtain translation of the source with our currently available institutional resources, the source will be excluded.

- Preclinical studies that include models of alcohol use with or without comorbid sleep disruption, stress/
Studies that report on oral microbiome and include analyses must contain associations between the bacterial communities of the oral microbiome, the methods used to measure alcohol use, neuropsychological disorders and the oral microbiome, and the possible translational applications and future directions of this research.

<table>
<thead>
<tr>
<th>Overarching objective</th>
<th>Subquestions/research objectives</th>
</tr>
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<tbody>
<tr>
<td>Examine research on the relationship between the oral microbiome and alcohol use, along with common co-occurring symptoms/diagnoses in alcohol use disorder: anxiety, depression, sleep disturbance and stress-related disorders. Based on the findings of this scoping review, we hope to gain insight into the extent of how alcohol use and neuropsychological disorders are associated with bacterial communities of the oral microbiome, the methods used to measure alcohol use, neuropsychological disorders and the oral microbiome, and the possible translational applications and future directions of this research.</td>
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</table>

<table>
<thead>
<tr>
<th>Objective</th>
<th>Proposed action</th>
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<tbody>
<tr>
<td>Identify research that studies the oral microbiome in association with alcohol use or alcohol use disorder, anxiety, depression, sleep disturbance and post-traumatic stress disorder</td>
<td>Compile all references and source material focused the oral microbiome association with alcohol use and alcohol use disorder. Annotate references that also include symptoms of or diagnosed anxiety, depression, sleep disturbance and post-traumatic stress disorder.</td>
</tr>
<tr>
<td>Present how alcohol use disorder, anxiety, depression, sleep disturbance and post-traumatic stress disorder has been studied in the context of the oral microbiome</td>
<td>Categorise different neuropsychological symptoms/disorders, associated interventions and operational definitions (see table 1). For each disorder, evaluate each instrument and metric of reporting.</td>
</tr>
<tr>
<td>Analyse research methodologies used and whether they are sufficient in characterising alcohol intake characterisation, alcohol use disorder, other neuropsychological symptoms or disorders, and oral microbiome community changes</td>
<td>Identify and report metrics and instruments used to quantify neuropsychological disorder and symptoms. Likewise, organise and compare the analysis strategies and measures used to characterise the bacterial and functional oral microbiome community structure.</td>
</tr>
<tr>
<td>Illustrate global and specific bacterial oral microbiome changes (and their byproducts) associated with alcohol use disorder, anxiety, depression, sleep disturbance and post-traumatic stress disorder</td>
<td>Synthesise preclinical and translational research examining associations between alcohol use, neuropsychological disorders and the oral microbiome and systematically present results to enable comparison and interpretation across studies.</td>
</tr>
</tbody>
</table>

PTSD, anxiety and depression will be considered if measures of the oral microbiome are included.

- For translational studies, analyses must contain associations between the bacterial oral microbiome and alcohol use. Studies that also examine the predefined alcohol-associated neuropsychological disorders and/or symptoms (ie, stress, PTSD, anxiety, depression, sleep disruption) in addition to alcohol use will be included.

- Studies that report on oral microbiome and include another microbiome niche (ie, gut) will be included, but only oral microbiome results will be reported in the data extraction table and scoping review.

**Exclusion criteria**

Review articles, outcomes not related to microbiome or analyses of microbiome and relevant neuropsychiatric diagnoses/symptoms not performed, outcomes related to other oral microbiome organisms (virus, protozoa, archaea, etc), additional intervention not associated with the oral microbiome simultaneously employed, other model organisms in preclinical research, and unable to obtain English language version of source with institutional resources.

**Information sources**

We worked closely with our institutional medical research librarian (GB) through multiple planning meetings and continued communication to develop and refine our search strategy through an iterative process. Overall broad search strategy, general search terms and MeSH terms were discussed and refined so appropriate terms and pertinent databases could be identified. The search strategy and methods were peer reviewed by a team consisting of medical librarians independent of the scoping review team to improve validity and reproducibility. The databases listed below will be used to identify sources of evidence, and reference lists will additionally be searched while reviewing papers to source relevant literature.

**Databases searched**

- PubMed/MEDLINE (National Library of Medicine)
- Embase (Elsevier)
- PsycINFO (American Psychological Association)
- Web of Science: Core Collection (Clarivate Analytics)
- CENTRAL trials database (Wiley & Sons)
- BIOSIS Citation Index (Clarivate Analytics)
- Zoological Record (Clarivate Analytics)

No limitations will be placed on the year of publication. Grey literature sources, such as medRxiv and bioRxiv preprint servers, will also be searched.

**Search strategy**

**Search terms**

Our research team met and developed initial search terms to capture data sources covering the full scope...
of the intended aims including different iterations of the oral microbiome, and clinical phenotype of interest (alcohol use/abuse, depression, stress, anxiety and sleep disturbance). For a full list of search terms and individual database search strategies, see online supplemental table 1.

Study records
Data management
All information sources identified by the medical research librarian in the database search will be imported in Covidence systematic review screening software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Duplicate sources will be removed, and title/abstract screening will be performed in Covidence. The primary sources that pass initial screening that will be included in the full-text review will have PDF versions of the data source uploaded into Covidence by the medical research librarian. The medical research librarian will construct naming conventions for the uploaded PDF files for clear identification of the source with an abbreviated title and year of publication. Data extraction worksheets will be designed in Covidence using the data extraction template version 2.0. Data from the extraction templates will be exported to csv format after completion by each source reviewer and will be stored on a cloud-based storage system. Copies will be downloaded for back-up regularly (at least weekly) on an institutional server. KM will be responsible for managing the data resulting from the literature search and screening review during the data collection process, and storing backups of all collected data after the project is completed.

Selection process
Study selection will be a collaborative process that will involve several rounds source screening including the initial removal of duplicates by the medical research librarian and then title/abstract and full text screening by the study team to determine relevance and fit for the aims of the scoping review. Two researchers (KM and CC) will screen all the sources independently in Covidence selected using the predefined inclusion and exclusion criteria outlined in this protocol paper and any discrepancies will be reviewed by a third researcher (GRW). Full agreement to include a source will be required across all reviewers before a final decision is made to include a source. Prior to initiating screening and importing all sources into Covidence, a ‘pilot’ of the protocol will be performed by the two primary reviewing researchers where 50 randomly selected records will be uploaded to ensure both screeners had a shared understanding of the inclusion and exclusion criteria, along with discussing and confirming the pertinent data that will be entered into the data extraction form from studies that will meet inclusion criteria. A group meeting with all authors (KM, CC, GB and GRW) will occur after the pilot is completed to review and discuss decisions made with the pilot screening results to ensure there is consensual agreement about screening and inclusion/exclusion criteria. The reviewers will meet regularly to discuss consistency of their screening and data extraction form, any obstacles in data extraction and revising the form if needed as additional microbiome or microbiome-associated biomarker outcome categories are identified, resolving disagreements through discussion. The study screening and reasons for excluding sources, along with the number of sources meeting inclusion/exclusion criteria at each screening stage will be illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in the scoping review paper, along with the final number of included primary sources.

Data collection process
After the final primary sources are selected for the scoping review, data will be systematically compiled using a data extraction form. Data charting will be performed by two team members using the data extraction form built in Covidence, and results will be compared with ensure data abstracted from the included sources is consistent with the overarching research objectives and research questions. Data charting will be discussed in a group setting with other members of the research team as needed or if questions arise.

Data items and outcomes
Key pieces of information from each study (author, year, aim of paper, population, main measures of interest) will be collected in a standard format in the data extraction form and will be presented in table format in the scoping review paper. Based on several meetings and discussions with the research team, we developed a priori targeted alcohol-comorbid symptoms and disorders that will be studied in addition to AUD (table 1). This is important, as we aim to understand not only oral microbiome implications/associations with alcohol use and AUD, but also the complex and overlapping clinical presentation that occurs in these subjects. The included studies will be organised according to the type of disorder or symptom being studied, the microbiome and microbial-associated metrics reported, and preclinical and translational studies will be reported separately. Human and animal studies will be grouped based on participant type (human or rodent), and the results from the rodent studies will be used to supplement themes identified from the clinical translational data in terms of symptoms and patient phenotype. Participant characteristics and demographic factors, such as age, sex, gender identity, medical comorbidities, medication use, drug use (ie, cannabis) and tobacco use will be collected during data extraction. Alcohol-associated variables such as alcohol consumption amount (ie, average drinks per day, average drinks per week), type of alcohol consumed, years of drinking, age of first drink and any diagnoses of AUD will be used to characterise the range of alcohol intake phenotypes across the studies and stratify results across different levels of alcohol use. Environmental factors that could influence the oral microbiome via different exposures (ie, pollution,
chemical exposures) will be recorded in the data extraction form including food environment, green space and other social determinants of health. We will also note in our data extraction form if environmental-level variables are not included in the study. We will include important microbiome associated study design and analysis considerations in the data extraction including DNA extraction methods, microbiome sequencing methodology used (ie, 16S ribosome RNA amplicon sequencing or shotgun metagenomics sequencing), and both pre-processing and downstream microbiome analyses. A non-exhaustive list of the microbiome and microbiome-associated biomarkers such as cytokines or metabolites are outlined in table 1. Data extraction will be performed within the Covidence programme using their data extraction form by two members of the study team (KM and CC), and any discrepancies identified by Covidence in the extracted data will be reviewed and discussed by the entire team before final inclusion in the synthesis table. The data columns included in the data extraction form and associated output will be iteratively reviewed by the study team and if it is determined that a key piece of information is not captured with the currently available data extraction format, an additional item to the data extraction form will be added. If additional items are added, previously reviewed studies will be re-examined to identify if new data needs to be added to the data extraction forms and output.

### Risk of bias in individual studies

One anticipated bias is the selective reporting of microbiome metrics across research studies reporting microbiome data, and the limited number of published studies that focus on alcohol-comorbid neurophysiological disorders and the oral microbiome. To overcome this bias, we will collect all diversity (alpha and beta) metrics, individual taxonomic-based metrics and functional/metabolicomic data in the synthesis table and supplemental data, while selected relevant metrics informed by KM’s expertise in the microbiome field will be emphasized in the scoping review text. We also will include data on the study population, phenotypes examined, sample size and intervention used, if applicable, so the synthesis of data can be examined considering the populations or groups studied.

### Synthesis of results

The purpose of this scoping review will be to aggregate overarching findings and relationships of oral microbiome bacterial communities and relevant oral microbiome-associated biomarkers with AUD and AUD-comorbid diagnoses and symptoms to start to understand mechanisms underlying oral-brain communication in this population. Microbiome and biomarker metrics will be compiled in a standard format in both preclinical and translational studies to allow for comparison of similarities and differences between phenotypes and models of disease. As we likely cannot assume directionality between AUD and AUD-comorbid disorders with the microbiome metrics in most studies (as they may be observational and/or cross-sectional), we will focus on associations between symptoms/diagnoses of interested listed in table 1 and the oral microbiome instead of attempting to identify causality in the outcome measures. Main results will be summarised, and the limitations and potential biases of the scoping review process will be discussed. The PRISMA Extension for Scoping Reviews will be used to facilitate reporting of the search strategy, source selection and analysis/synthesis of primary sources in the scoping review paper.95

We hypothesize the overall mechanisms/themes that will be relevant in oral microbiome signalling and alcohol-comorbid disorders will include inflammatory-associated mechanisms, metabolite-associated mechanisms (ie, short chain fatty acids, bile acids, etc) and stress-signalling associated mechanisms (ie, hypothalamic-pituitary-adrenal axis signalling). Additionally, a qualitative analysis of patterns emerging from the extracted data and reported results will be examined to define potential mechanistic pathways that can be tested in future hypothesis-driven research. Areas of agreement and disagreement across primary source literature, along with gaps in the literature will be presented to identify areas where future research or study replication is needed to build on this area of research.

### Patient and public involvement

None.

### ETHICS AND DISSEMINATION

We present a scoping review protocol with the overarching aim to examine research on the relationship between the oral microbiome and neuropsychological disorders with a specific focus on AUD and common co-occurring symptoms/diagnoses in AUD including anxiety, depression, sleep disturbance and stress-related disorders. The proposed scoping review will be based on the analysis of publicly available literature databases and primary sources, and thus does not require human subjects or ethical approval. Our goal to extract, compile and synthesise primary sources of evidence emphasising the oral microbiome that will hopefully allow us to identify to what extent this research has been undertaken, what specific symptoms or AUD-associated diseases have been studied, and what instruments or models have been used to conduct this research. We hope to not only present a comprehensive synthesis of the state of the current science, but also assist researchers in identifying commonly used metrics and gaps in the science to facilitate comparisons across studies and future research. We expect the results of this synthesis will identify gaps in the small but growing literature in this field and highlight potential mechanisms linking the oral-brain axis to addiction and other associated neuropsychological conditions. Furthermore, we seek to provide a synthesis of evidence that can assist in hypothesis generation for future translational clinical research aimed at improved outcomes in individuals with AUD. We plan to discuss the overarching themes and synthesised study results with stakeholders including clinicians and collaborating researchers who work with this patient population to ensure we are capturing themes appropriately. The study findings and results will be disseminated through journals and conferences related to
addiction medicine, psychology, immunology, neuroscience, dentistry, bioinformatics and the microbiome.

Twitter Katherine A. Maki @Katherine_Maki1

Contributors Study concept: KM and GRW. Protocol design: KM, CC, GB and GRW. Initial draft: KM and CC. Critical revisions: GB and GRW. Approved final paper: KM, CC, GB and GRW. KM serves as the guarantor of the review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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26 Roehrs T, Roth T. Insomnia as a path to alcoholism: tolerance development and dose escalation. Sleep 2018;41:zay091.


101 Su X. Elucidating the beta-diversity of the microbiome: from global alignment to local alignment. *mSystems* 2021;6:e0036321.
## Supplemental Table 1. Representative Example of Literature Search Terms Stratified by Concept of Interest

### Database Search Strategies

**Database:** PubMed/MEDLINE  
**Platform:** National Library of Medicine  
**Date Searched:** 9/29/2023  
**Limits:** Editorial, commentary, retraction, review

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#4 Limits

Database: Cochrane CENTRAL
Platform: Wiley & Sons
Date Searched: 9/29/2023
Limits: Editorial, commentary, retraction, review

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<td><strong>Microbiome</strong></td>
<td>[mh &quot;Microbiota&quot;] OR microbio* OR microflora* OR [mh &quot;Dysbiosis&quot;] OR dysbio* OR disbio* OR [mh &quot;Gastrointestinal tract&quot;/MI] OR [mh &quot;RNA, Ribosomal, 16s&quot;] OR &quot;16S&quot; OR shotgun OR [mh &quot;Metagenomics&quot;] OR</td>
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### Concept Search Strategy

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#3 Depression, Stress and Anxiety + Alcohol

'depression'/exp OR 'anxiety'/exp OR 'anxiety disorder'/exp OR 'panic'/exp OR 'psychologic test'/exp OR 'questionnaire'/de OR 'patient health questionnaire'/exp OR 'mood disorder'/de OR 'sleep'/exp OR 'posttraumatic stress disorder'/exp OR 'mental stress'/de OR 'mental disease'/de OR 'posttraumatic stress disorder'/de OR 'alcoholism'/de OR 'depress*':ab,ti OR 'neuropsycholog*':ab,ti OR 'neuro psychosis*':ab,ti OR 'neuro psychiatri*':ab,ti OR 'neuro-anxiety*':ab,ti OR 'neuropsychiatr*':ab,ti OR 'neuro-psychiatr*':ab,ti OR 'anxiety*':ab,ti OR 'panic disorder*':ab,ti OR 'panic attack*':ab,ti OR 'mood disorder*':ab,ti OR 'psychological stress*':ab,ti OR 'stress disorder*':ab,ti OR 'chronic NEAR/6 stress' OR 'sleep*':ab,ti OR 'asleep*':ab,ti OR 'post-traumatic stress disorder*':ab,ti OR 'ptsd':ab,ti OR 'mental disorder*':ab,ti OR 'mental illness*':ab,ti OR 'psychological test*':ab,ti OR 'psychological exam*':ab,ti OR 'psychological assessment*':ab,ti OR 'patient health questionnaire*':ab,ti OR 'neuropsychological test*':ab,ti OR 'neuro-psychological test*':ab,ti OR 'dental health survey*':ab,ti OR 'alcohol use*':ab,ti OR 'alcohol dependent*':ab,ti OR 'alcohol abuse*':ab,ti OR 'alcohol addiction*':ab,ti OR 'alcoholism*':ab,ti OR 'alcoholic*':ab,ti OR 'binge drink*':ab,ti

#4 Limits

#1 AND #2 AND #3 NOT ('editorial'/exp OR 'letter'/exp OR 'news'/exp OR 'practice guideline'/exp OR guideline*:ti OR [review]/lim OR [systematic review]/lim OR 'systematic review':ab,ti OR 'review':ti OR [meta analysis]/lim OR 'meta analysis':ti OR 'meta-analyses':ti OR 'retraction of publication':ab,ti OR 'retracted publication':ab,ti OR 'retraction notice':ti)
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<td>TS=(mouth OR tongue OR oral OR saliva OR salivary OR dental* OR plaque* OR interdental* OR periodontal* OR gingival* OR supragingival* OR subgingival* OR tongue* OR periodontitis OR gingivitis OR gingiva)</td>
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<tr>
<td>#2 Microbiome</td>
<td>TS=(microbio* OR microflora* OR dysbio* OR disbio* OR &quot;16S&quot; OR shotgun OR metagenom* OR &quot;bacterial protein*&quot; OR biofilm* OR &quot;anaerobic bacteria*&quot; OR &quot;DNA sequence analy*&quot; OR &quot;bacterial DNA&quot;)</td>
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<td>#3 Depression, Stress and Anxiety + Alcohol</td>
<td>TS=(depress* OR neuropsycholog* OR neuro-psycholog* OR neuropsychiatr* OR neuro-psychiatr* OR anxiet* OR anxious* OR &quot;panic disorder*&quot; OR &quot;panic attack*&quot; OR &quot;mood disorder*&quot; OR &quot;psychological stress*&quot; OR &quot;stress disorder*&quot; OR (chronic NEAR/6 stress) OR sleep* OR asleep* OR &quot;post-traumatic stress disorder*&quot; OR &quot;PTSD&quot; OR &quot;mental disorder*&quot; OR &quot;mental illness*&quot; OR &quot;psychological test*&quot; OR &quot;psychological exam*&quot; OR &quot;psychological assessment*&quot; OR &quot;Patient Health Questionnaire* OR &quot;neuropsychological test*&quot; OR &quot;neuro-psychological test*&quot; OR &quot;Dental Health Survey*&quot; OR &quot;alcohol use*&quot; OR &quot;alcohol dependen*&quot; OR &quot;alcohol abus*&quot; OR &quot;alcohol addiction*&quot; OR &quot;alcoholism* OR alcoholic* OR &quot;binge drink*&quot;)</td>
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<td>#4 Limits</td>
<td>(#3 AND #2 AND #1) NOT Book OR Book Chapter OR Book Review OR Editorial Material OR Item Withdrawal OR Letter OR Note OR Retracted Publication OR Retraction OR Review OR Withdrawn Publication (Document Type) and Web of Science Core Collection (Database)</td>
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Database: BIOSIS Citation Index  
Platform: Clarivate Analytics  
Date Searched: 9/29/2023  
Limits: Editorial, commentary, retraction, review

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Database: Zoological Record  
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Date Searched: 9/29/2023  
Limits: Editorial, commentary, retraction, review

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<tr>
<td>Depression, Stress and Anxiety + Alcohol</td>
<td>TS=(depress* OR neuropsycholog* OR neuro-psycholog* OR neuropsychiatr* OR neuro-psychiatr* OR anxiet* OR anxious* OR &quot;panic disorder*&quot; OR &quot;panic attack*&quot; OR &quot;mood disorder*&quot; OR &quot;psychological stress*&quot; OR &quot;stress disorder*&quot; OR (chronic NEAR/6 stress) OR sleep* OR asleep* OR &quot;post-traumatic stress disorder*&quot; OR &quot;PTSD&quot; OR &quot;mental disorder*&quot; OR &quot;mental illness*&quot; OR &quot;psychological test*&quot; OR &quot;psychological exam*&quot; OR &quot;psychological assessment*&quot; OR &quot;Patient Health Questionnaire&quot; OR &quot;neuropsychological test*&quot; OR &quot;neuro-psychological test*&quot; OR &quot;Dental Health Survey*&quot; OR &quot;alcohol use*&quot; OR &quot;alcohol dependent*&quot; OR &quot;alcohol abus*&quot; OR &quot;alcohol addiction*&quot; OR alcoholism* OR alcoholic* OR &quot;binge drink&quot;)</td>
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Date Searched: 9/29/2023

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